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Obesity and dyslipidemia

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ABSTRACT

Obesity, a pandemic of the modern world, is intimately associated with dyslipidemia, which is mainly driven by the effects of insulin resistance and pro-inflammatory adipokines. However, recent evidence suggests that obesity-induced dyslipidemia is not a unique pathophysiological entity, but rather has distinct characteristics depending on many individual factors. In line with that, in a subgroup of metabolically healthy obese (MHO) individuals, dyslipidemia is less prominent or even absent. In this review, we will address the main characteristics of dyslipidemia and mechanisms that induce its development in obesity. The fields, which should be further investigated to expand our knowledge on obesity-related dyslipidemia and potentially yield new strategies for prevention and management of cardiometabolic risk, will be highlighted. Also, we will discuss recent findings on novel lipid biomarkers in obesity, in particular proprotein convertase subtilisin/kexin type 9 (PCSK9), as the key molecule that regulates metabolism of low-density lipoproteins (LDL), and sphingosine-1-phosphate (S1P), as one of the most important mediators of high-density lipoprotein (HDL) particles function. Special attention will be given to microRNAs and their potential use as biomarkers of obesity-associated dyslipidemia.

Contents

Abbreviations: FFAs, free fatty acids; LPL, lipoprotein lipase; sdLDL, small, dense low-density lipoprotein; TNF-α, tumor necrosis factor-α; PCSK9, proprotein convertase subtilisin/kexin type 9; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; S1P, sphingosine-1-phosphate.

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1. Introduction

Weight gain, as a response to overnutrition and reduced energy expenditure, leads to overweight and obesity, conditions associated with intensive processes of hyperplasia and hypertrophy of adipocytes [1]. Also, obesity is accompanied by macrophages infiltration into the adipose tissue, followed by a switch of their phenotype from anti-inflammatory M2 to pro-inflammatory M1 [2]. All these changes in adipose tissue composition are associated with altered adipokines secretion and development of adipose tissue dysfunction (adiposopathy) which is responsible for obesity-related metabolic diseases [3].

Insulin resistance/hyperinsulinemia is the most common metabolic disorder in obesity and it is the main driving force behind the development of dyslipidemia. In recent years, the form of dyslipidemia arising from concerted action of insulin resistance and obesity is recognized as "metabolic dyslipidemia" [4]. High concentrations of triglycerides (TG) accompanied by decreased high-density lipoprotein cholesterol (HDL-C) concentrations are its main characteristics. Low-density lipoprotein cholesterol (LDL-C) concentrations could be optimal or mildly increased, although the number of LDL particles (LDL-P) can be increased [5]. Dyslipidemia is an important link between obesity and the development of type 2 diabetes mellitus, cardiovascular disease (CVD) and certain types of cancer [6].

2. Pathways of metabolic dyslipidemia development

Accumulating evidence suggests that insulin resistance is the most probable link between obesity and obesity-associated metabolic dyslipidemia [4]. According to Magkos et al. [7] insulin resistance and metabolic dyslipidemia are associated with adiposopathy. As previously demonstrated, adiposopathy is characterised by several structural and functional changes in adipose tissue [2,3]. These abnormalities also have detrimental effects on adipocyte intracellular structure, leading to endoplasmic reticulum stress and dysfunction of mitochondria [8]. Generally, it is accepted that the most important molecular mediators of obesity-related insulin resistance are adipokines, produced by adipocytes and accumulated macrophages in adiposopathy [9]. Moreover, changed adipocytes are insulin-resistant, which increases lipolysis and release of free fatty acids (FFAs) into the circulation. Increased FFAs concentration provokes lipotoxicity, as another mechanism of obesity-related insulin resistance in non-adipose tissue [10].

2.1. Insulin resistance

Effects of insulin on lipid metabolism are known and well explained [4]. Insulin suppresses lipolysis in adipose tissue by hormone-sensitive lipase (HSL) inhibition, thereby controlling the release of FFAs into the circulation [11]. Also, insulin stimulates apolipoprotein B-100 (apoB-100) degradation and suppresses very low-density lipoproteins (VLDL) secretion from the liver [12]. In the circulation, lipoprotein lipase (LPL)-driven hydrolysis of TG from VLDL particles is stimulated by insulin, as well as the activity of hepatic lipase (HL), so overall, insulin stimulates TG-rich lipoprotein degradation. In the liver, insulin promotes dephosphorylation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, activating the enzyme and stimulating the rate of cholesterol synthesis [11]. In the state of insulin resistance, plasma clearance of TG-rich lipoproteins is delayed, resulting in hypertriglyceridemia. Under these circumstances, cholesteryl ester transfer protein (CETP) activity promotes the exchange of TG with cholesteryl esters between lipoprotein particles. As a result, LDL and HDL particles become enriched with TG and, after subsequent hydrolysis by plasma lipases, smaller and denser. These structural changes are accompanied by functional consequences, resulting in the accumulation of small, dense (sdLDL) and dysfunctional HDL particles [13].

The role of FFAs in obesity-related insulin resistance development has also been documented. Some authors emphasize that the increased release of FFAs from adipose tissue could be the first step in this cascade process [14]. FFAs in hypertrophic adipocytes activate specific serine-kinases which are responsible for phosphorylation of Insulin Receptor Substrates (IRS) proteins, and this covalent modification reduces insulin receptor signalling [15]. Also, it is known that FFAs are ligands for several cellular receptors that are involved in the cellular immune response [16]. Binding of FFAs to Toll-like receptor 4 (TLR 4) on pro-inflammatory M1 macrophages induces productions of pro-inflammatory adipokines and stimulates inflammation in adipose tissue [17,18]. Insulin-resistant adipocytes release FFAs into the circulation. Normally, FFAs are utilized either for biosynthesis of complex lipid molecules or for oxidation in different tissues. When the capacities of these two metabolic pathways become saturated, the content of FFAs and their metabolic intermediates increase in the cell, leading to ectopic lipid accumulation and insulin resistance development in liver and skeletal muscle [19]. Increased FFAs flux into the hepatocytes alters glucose metabolism, via hepatic insulin resistance development, but also, by insulin-independent mechanism. Intensive FFAs catabolism in liver increases acetyl-CoA, an allosteric activator of pyruvate carboxylase, which stimulates gluconeogenesis. These processes lead to hyperglycemia and consequent hyperinsulinemia [19,20].

2.2. Adipokines

Adipokines have many different metabolic functions and their role in pathophysiological conditions associated with obesity has been the main topic of numerous studies during the last two decades. Special interest has been focused on their inflammatory aspects [21,22].

2.2.1. Pro-inflammatory adipokines and dyslipidemia

The discovery of leptin, the product of obesity (ob) gene, and its role in the regulation of food intake and energy expenditure was the breakpoint of the concept that adipose tissue is an active endocrine organ [23]. Association of leptin and insulin resistance was observed in leptin-deficient (*ob*/*ob*) mice and exogenous administration of leptin improved insulin resistance [24]. Leptin and insulin have similar general effects on lipid metabolism (Table 1). It is known that leptin participates in the negative feedback loop that reduces insulin secretion, but it also stimulates glucose turnover which improves insulin sensitivity [21]. Leptin is considered a pro-inflammatory adipokine since it stimulates adipose tissue macrophages to secrete tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), interleukin 12 (IL-12) and potentiates low-grade inflammation in adipose tissue [24]. Despite the fact that leptin exhibits pro-inflammatory effect, currently it has therapeutic application in patients with generalized lipodystrophy [25]. Perry et al. [25] showed that leptin reduced glucose concentrations in rodents with poorly controlled type 1 diabetes, by a suppression of hypothalamic-pituitary-adrenal (HPA) activity and consequent reduction of gluconeogenesis and ketogenesis. This result qualifies leptin as a potential new adjuvant therapy in type 1 diabetes and indicates the need for further investigations.

Resistin is an adipokine primarily secreted by macrophages and monocytes in humans and its role in insulin resistance development is not completely clear. Generally, it is accepted that resistin reduces insulin sensitivity in humans, but the results of numerous studies are not uniform. Clinical studies found no correlations between resistin concentration and indices of insulin resistance or obesity [22]. However, there is no doubt that resistin plays a role as a direct molecular mediator of metabolic dyslipidemia development (Table 1). The role of resistin in inflammation is also well known. Inflammatory cytokines stimulate macrophages to secrete resistin by induction of resistin gene expression, while resistin, in turn, promotes the production of pro-inflammatory cytokines [22].

TNF-α is a multipotent cytokine, involved in all aspects of obesity-induced insulin resistance and dyslipidemia development (Table 1). The main mechanism which connects inflammation, particularly TNF-

Table 1
Relevant adipokines and their effects on lipid metabolism

Adipokine	Mechanisms of action	Effects on lipid metabolism
Pro-inflammatory adipokines		
Leptin [21]	Activation of FFAs oxidation enzymes Decrease of TG storage in non-adipose tissues	Lipolytic effect
Resistin [26]	Activation of microsomal triglyceride transfer protein (MTP) Stimulation of apoB-100 synthesis	Increased VLDL production
	Increase of proprotein convertase subtilisin/kexin type 9 (PCSK9) level	Downregulation of hepatic LDL receptor expression
TNF-α [27]	Phosphorylation and activation of hormone-sensitive lipase (HSL)	Lipolytic effect
IL-6 [30]	Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and activator of the Mitogen-Activated Protein Kinase (MAPK) cascade	Lipolytic effect
IL-1 [31]	Suppresion of lipoprotein lipase (LPL) activity	Hypertriglyceridemia
Anti-inflammatory adipokines		
IL-10 [34]	PPAR-γ-dependent ATP-binding cassette transporter 1 (ABCA1)-mediated cholesterol efflux to apolipoprotein A1	Increased HDL-C concentration
Adiponectin [35]	AMPK-activated PPARα transcription factor	Increased FFAs oxidation
Omentin 1 [36]	Activation of AMPK signalling pathway	Inhibition of cholesterol synthesis

α and IL-6, with insulin resistance is a reduced expression of glucose transporter type 4 (GLUT 4) in insulin-dependent tissues under their influence [28]. Also, TNF-α activates serine-kinases responsible for phosphorylation of IRS, specifically Jun N-terminal kinase (JNK) [29]. The specific effect of TNF-α is related to the acceleration of the inflammatory process by induction of synthesis of other pro-inflammatory cytokines, such as IL-6 and IL-1, in the macrophages of adipose tissue. It is also important to note that TNF-α, in cooperation with other inflammatory cytokines (Table 1), induces the activation of the NF-κB pathway and promotes oxidative stress in adipose tissue [32]. Activation of the NF-κB transcription factor by TNF-α is one of the mechanisms which induces inflammation of β-cells and leads to reduced insulin production [33].

2.2.2. Anti-inflammatory adipokines and dyslipidemia

Among anti-inflammatory adipokines (Table 1), adiponectin has the highest concentration in plasma. In adyposopathy, TNF-α, IL-6 and reactive oxygen species downregulate the expression of *ADIPOQ* gene in adipocytes, so the level of adiponectin in the circulation is decreased. The most important mechanisms by which adiponectin enhances insulin sensitivity seems to be via the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-α (PPAR-α) [35], a transcription factor that regulates lipid metabolism in the liver (Table 1). The main effects are the increased FFAs oxidation and glucose uptake in muscle and the inhibition of hepatic glucose production [37]. Adiponectin also directly influence β-cell function, exerting anti-apoptotic effects [38]. The results of several studies connected adiponectin with the decreased apolipoprotein AI (apoAI) catabolism and higher HDL-C concentrations in plasma [39]. Qiao et al. [40] showed that adiponectin reduces TG concentration in plasma and the underlying mechanism of this effect is the increased activity of LPL, via increased LPL gene expression in skeletal muscle. Adiponectin has also potent anti-inflammatory effects within adipose tissue [41].

Finally, it is interesting to mention specific adipokine Sfrp5, a member of Sfrp inhibitors of wingless-type MMTV integration site family, especially Wnt 5a [42]. Experiments on mouse models proved that Sfrp5 protein is a powerful anti-inflammatory adipokine [43]. Sfrp5 inhibits Wnt 5a-mediated phosphorylation of JNK in adipose tissue and this change in signalling pathway is associated with lower macrophages accumulation in adipose tissue. However, it is not clear whether similar relations exist in humans. The pioneering research of Sfrp5 in humans, concerning its association with the development of insulin resistance gave controversial results, ranging from positive association to no association at all [42,44]. Recently published results of the population-based KORA study showed that Sfrp5 concentration was independently associated with HDL-C, glycated haemoglobin, high sensitivity C-reactive protein and adiponectin concentrations [45]. The observed association between high Sfrp5 and high HDL-C concentrations indicates possible influence of this adipokine on lipid metabolism, but a concrete mechanism is not yet clarified.

2.3. Vitamin D and dyslipidemia in obesity

High prevalence of vitamin D deficiency in obese individuals is well known and confirmed by many investigations. Yet, the exact mechanism which is responsible for this association is still unrevealed. Several hypotheses are proposed and all of them can be classified into three categories. Preliminary theories were based on the associations of vitamin D with anthropometric, physiological and behavioural characteristics of obesity. The ground for second group of hypotheses is the concept which relays on the interplay between dyslipidemia and vitamin D. Finally, the third group of presumptions points towards the crucial role of obesity-related inflammation (Fig. 1). However, a common feature of all above mentioned theories is that vitamin D deficiency is more likely the effect of obesity than its cause. Nevertheless, lack of vitamin D is associated with many unfavourable metabolic aspects of obesity, forming a vicious cycle that finally leads to increased cardiometabolic risk (Fig. 1).

A bulk of evidence suggests that adipose tissue is a direct target for vitamin D actions, in term of modulation of adipogenesis, apoptosis and inflammatory pathways [46–50]. It has been demonstrated that vitamin D exhibits apoptotic effects on adipocytes [51]. Having in mind recent discovery of autonomous bioactivation of this hormone in adipocytes [52], markedly increased amount of vitamin D in adipose tissue may have potential protective effects by preventing hyperplasia of adipocytes. Contrary to studies on mouse cell lines demonstrating inhibitory effects of vitamin D on adipogenesis, Nimitphong et al. [53] showed that vitamin D promotes differentiation of human preadipocytes to mature well-differentiated, insulin-sensitive adipocytes, hypothesizing the role of vitamin D in the healthy remodelling of adipose tissue.

2.3.1. Vitamin D and lipid profile

Up till now, a significant number of observational and interventional studies have been conducted in order to elucidate the interplay between vitamin D deficiency and dyslipidemia, as well as possible therapeutic implications. However, it is still difficult to draw a definitive conclusion regarding the relationship of vitamin D metabolites with serum lipids. A large cross-sectional study by Jorde et al. [54] demonstrated an increase in TC and LDL-C levels across increasing quartiles of 25(OH)D. Conversely, a more recent study by Lupton et al. [55], which included more than 20,000 participants, showed significant associations of vitamin D deficiency with higher concentrations of TC and LDL-C. A Mendelian randomization study by Ooi et al. [56] demonstrated that genetically elevated levels of nonfasting remnant cholesterol are related to decreased vitamin D concentrations, but without

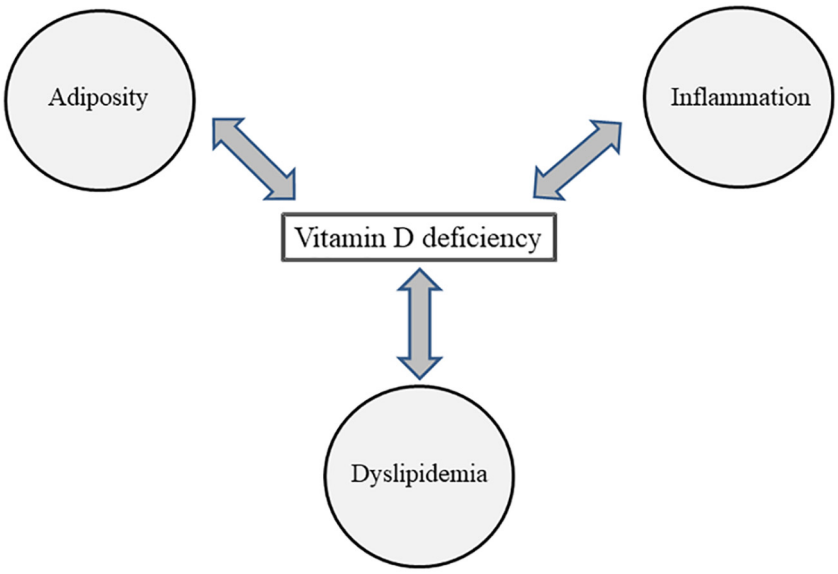

Fig. 1. Possible mechanisms of the associations between obesity and vitamin D deficiency.

evidence for the impact of inherited vitamin D deficiency on cholesterol concentration. Such results suggest that low vitamin D is more likely a marker of dyslipidemia than its contributing factor. The same research [56] demonstrated that genetically low HDL-C levels are associated with higher concentration of 25(OH)D. Similarly, the findings of the Rotterdam study [57] pointed toward inverse and, even more importantly, bidirectional associations between HDL-C and vitamin D plasma levels, suggesting the possible direct impact of vitamin D on HDL metabolism. Finally, previous studies generally pointed toward negative correlations between vitamin D and TG concentrations [58].

Vitamin D and cholesterol share the same biosynthetic pathway since 7-dehydrocholesterol is their joint precursor. Therefore, it has been suggested that the increase in cholesterol biosynthesis would cause a reciprocal decrease in 25(OH)D formation in the skin [57]. Such an assumption can provide an explanation for the previously reported increase in vitamin D level after statin therapy [59,60]. However, not all studies reported such findings and it has been as well demonstrated that statin use does not affect vitamin D levels [61,62]. On the other hand, Chow et al. [63] recently proposed that activation of vitamin D receptor (VDR) both in mice and human hepatocytes leads to enhanced activity of 7α-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis. As a result, parenteral treatment with 1,25(OH)$_2$D caused a decrease of plasma and liver cholesterol in mice [63], suggesting the active role of vitamin D in regulation of cholesterol homeostasis. Finally, one should not neglect the indirect effects of vitamin D, realized through the changes in calcium and parathyroid hormone (PTH) concentrations. Previous researches revealed that higher calcium input increases faecal fat excretion [64], alongside with favourable effects on plasma lipid profile [65,66]. Similarly, sufficient levels of vitamin D are necessary for preventing the development of hyperparathyroidism which is well-known contributor to adverse changes of lipid profile [67,68].

3. Metabolically healthy and metabolically unhealthy obesity — the role of dyslipidemia

Metabolically healthy obesity (MHO) is the term used to designate a subgroup of obese subjects without obvious detrimental consequences of increased weight [69]. In addition, a subset of lean subjects with metabolic disturbances has also been recognized and categorized as metabolically unhealthy normal weight subjects (MUNW) [70]. To date, numerous authors proposed various definitions of MHO, which could be summarised as the absence of the following metabolic disturbances: abdominal obesity, hypertension, dyslipidemia, hyperglycemia and/or insulin resistance. The most common approach to define metabolic health was based on the presence of less than two features of metabolic syndrome [71].

Routine serum lipid parameters are the most frequently evaluated components for distinguishing between MHO and metabolically unhealthy obese (MUO) subjects [72–77]. Albeit obese, MHO subjects are likely to have serum lipid parameters within the recommended range, similarly to metabolically healthy normal weight (MHNW) subjects. In contrast, pro-atherogenic changes are usually found in the lipid profile of MUO and MUNW subjects (Table 2). So far, a limited number of studies have evaluated the lipoprotein subclasses profile, mainly LDL particles, among MHO and MUO individuals. According to available data, MUO subjects have smaller LDL size, increased proportion of sdLDL particles and higher prevalence of LDL B phenotype [76,78,79]. Investigators of Women's Health Study followed 25,626 women for ten years and showed that obese women with dyslipidemia had increased CVD risk compared to obese women without dyslipidemia. The authors did not find the differences in CVD risk between obese and normal weight women without dyslipidemia [72]. Similarly, in the Danish prospective Diet, Cancer and Health study, it was found that obese participants with hypercholesterolemia have a higher risk for the acute cardiovascular event than obese or normal weight subjects without hypercholesterolemia [80].

In recent years more attention has been paid to improve the classification criteria for MHO, in attempt to direct appropriate preventive measures according to the anticipated risk [69,70]. Namely, in the meta-analysis of eight studies Kramer et al. [73] showed that MHO

Table 2
Lipid profile in metabolically healthy and unhealthy obese and normal weight subjects [72–77]

	Metabolically healthy		Metabolically unhealthy	
	Normal weight	Obese	Normal weight	Obese
TC	N	↔	↔	↔
LDL-C	N	↔	↑	↔/↑
HDL-C	N	↔	↓	↓↓
TG	N	↔	↑	↑↑
sdLDL	N	↔	↑	↑

In relation to metabolically healthy normal weight subjects (N, normal): ↔, unchanged; ↑, increased; ↓, reduced. TC; total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C; high-density lipoprotein cholesterol; TG, triglycerides; sdLDL, small, dense LDL.

subjects, when compared to MHNW peers, were not at increased risk of all-cause mortality and/or cardiovascular events. However, MHO was associated with the risk for long-term (≥10 years) adverse outcomes, suggesting the transient nature of this apparently healthy phenotype. More recent meta-analysis of Eckel and co-workers [74] evaluated data from 22 prospective studies and concluded that MHO subjects, regardless of the criteria used to define metabolic health, are at increased risk for cardiovascular events compared to MHNW subjects. Although based on limited data, this study also suggests that MHO might not increase cardiovascular risk for the limited period of time [74]. Thus, the work of both groups led to the same conclusion that MHO confers short-term protection against CVD development [73,74]. Of note, similar observations have been made about the risk for type 2 diabetes mellitus [81,82].

In general, MHO subjects are characterised by less visceral and/or ectopic fat accumulation, as well as by a lower extent of adipocyte dysfunction, as reviewed in detail in [83,84]. Compared to MHO, individuals with MUO have a higher degree of adipose tissue inflammation [71]. Regarding adipokines, results of Framingham Heart Study showed that MHO subjects had lower leptin and adiponectin levels [85]. Other studies found paradoxically higher adiponectin levels in adult MHO subjects [86–88] and adolescent females [89,90]. These data suggest protective role of higher adiponectin levels against obesity-associated metabolic diseases. Studies identified various genes involved in the regulation of adipogenesis and metabolic processes which may predispose to certain obesity pattern [87,91]. The investigations are further extended to epigenetic mechanisms which may be implicated in regulation of obese phenotypes. MicroRNAs (miRNAs) are small, single-strained, non-coding RNAs which regulate protein expression on post-transcriptional level, by blocking mRNA translation or forcing its degradation [92]. Numerous miRNAs are implicated in the regulation of adipogenesis, insulin resistance and inflammation [93,94]. A clear difference in miRNA profile of adipose tissue between lean and obese subjects has been shown [95], as well as in circulating miRNA levels between obese, overweight and control subjects [96,97], suggesting that miRNAs might be explored as biomarkers for distinguishing between MHO and MUO individuals.

4. Novel biomarkers of dyslipidemia in obesity

Over the last decade, the knowledge of the complex link between dyslipidemia and cardiovascular risk has been further expanded with the introduction of novel mechanisms and molecules, constituting potential biomarkers or therapeutic targets. Here, we will discuss obesity-related changes of two recently discovered biomarkers and modulators of LDL metabolism and HDL functionality, i.e. PCSK9 and sphingosine-1-phosphate (S1P), respectively. In addition, functional role of microRNAs and potential use of circulating microRNAs as novel biomarkers of dyslipidemia will be discussed.

4.1. Proprotein convertase subtilisin/kexin type 9 in obesity

PCSK9 is a glycoprotein, predominantly synthesized in hepatocytes, but also in enterocytes, as a zymogen, a preprotein that comprises 692 amino acid residues. It belongs to the proprotein convertase superfamily consisting of nine serine proteases [98]. PCSK9 has no enzymatic activity toward other substrates, except itself, enabling its own secretion in the circulation. However, the catalytic domain of PCSK9 is responsible for its binding to epidermal growth factor (EGF)-A domain of LDL receptor [99]. Following internalisation, PCSK9 impedes recycling of the receptor to the cell surface and enhances its lysosomal degradation (for more comprehensive reviews see [100,101]). There is also another type of interaction between PCSK9 and LDL receptor, which is termed intracellular pathway. In brief, intracellular binding of newly synthesized PCSK9 to LDL receptor fosters degradation of the complex in lysosomes which reduces the level of the receptors at the cell surface [102]. Therefore, the main role of PCSK9 is regulation of LDL receptor levels and, consequently clearance of LDL particles, so as plasma LDL-C level. Recent studies have pointed toward additional mechanisms of interactions between circulating PCSK9, LDL particles and LDL receptors (Fig. 2) including: regulation of both PCSK9 and LDL receptor synthesis via sterol regulatory element-binding protein-2 (SREBP-2) [103], bonding of circulating PCSK9 to LDL particles (approximately 30% of PCSK9) [104] and the impact of PCSK9 on secretion of VLDL particles [100]. The link between PCSK9 and CVD has been confirmed by the results of Mendelian randomization studies, documenting that individuals carrying certain loss-of-function *PCSK9* gene variants have a lower LDL-C level and reduced CVD risk [105]. Accumulating evidence on the role of PCSK9 in dyslipidemia led to the development of novel therapeutic PCSK9 inhibitors with convincing data about their efficiency and safety [106,107].

Available data on the effect of increased body weight on plasma PCSK9 levels and/or association between PCSK9 and obesity indices are scarce and inconclusive. Higher PCSK9 levels were found in obese, as compared to overweight and normal weight subjects [108,109]. Levenson et al. [110] reported that PCSK9 level was higher in obese women and those with type 2 diabetes, but not in obese and diabetic men. In the study of Hasan et al. [111] an inverse association between PCSK9 level and waist circumference in young females was found. In contrast, other groups reported positive correlations of PCSK9 with waist circumference and BMI [112]. As previously explained, insulin resistance and adipokines play major roles in the development of metabolic dyslipidemia. Studies with insulin resistant/deficient mice suggested that insulin enhances hepatic PCSK9 expression [113]. Although studies with animal models demonstrated up-regulation of hepatic PCSK9 expression during hyperinsulinemic-euglycemic clamp [114], clinical studies in healthy subjects and type 2 diabetic patients found no change [115] or even a decrease in plasma PCSK9 levels in obese postmenopausal women [116]. Cariou et al. [117] showed that PCSK9 concentration was positively associated with whole-body and hepatic insulin resistance. In line with the previous findings, large observational studies showed a positive correlation between circulating PCSK9 levels and HOMA-IR in both pediatric [118] and adult [119]

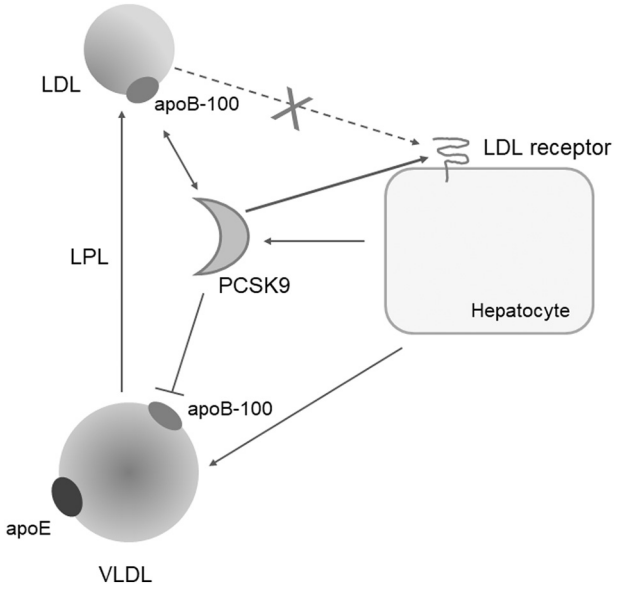

Fig. 2. Mutual relationships between PCSK9, VLDL and LDL particles and LDL receptors. Synthesis of PCSK9 and LDL receptor in the liver is regulated by SREBP-2. The main route of PCSK9 clearance is via LDL receptor. PCSK9 stimulates hepatic secretion of VLDL particles. Hepatic uptake of VLDL remnants following lipolysis in plasma depends on the LDL receptor. Circulating PCSK9 can attach to apoB-100 within LDL particles, but not to apoB-100 within VLDL. Bonding of PCSK9 to LDL particles diminishes its activity toward LDL receptor. PCSK9, proprotein convertase subtilisin/kexin type 9; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; LPL, lipoprotein lipase.

populations. A similarity in the PCSK9 and resistin structures has been revealed by Hampton et al. [120]. It was further demonstrated that resistin reduced LDL receptor, while in turn increased PCSK9 expression in HepG2 cells [121]. Surprisingly, Kwakernaak and colleagues [122] found that plasma PCSK9 level was inversely associated with resistin in lean and insulin sensitive subjects, while in overweight/obese and insulin resistant subjects PCSK9 was not related to resistin at all [122]. Regarding the role of leptin, it has been demonstrated that it suppresses LDL receptor level and LDL uptake but increases PCSK9 expression in HepG2 cells [123]. However, leptin replacement in male *ob*/*ob* mice decreased plasma PCSK9 level but had no effect on lipid parameters. In contrast, upon leptin administration in female mice, plasma lipids were reduced, while the level of PCSK9 remained unchanged [124]. On the other hand, treatment with a synthetic leptin analogue, metreleptin, reduced plasma PCSK9 levels in patients with lipodystrophy [124,125].

One of the mechanisms for a causal relationship between elevated PCSK9 and development of dyslipidemia in obesity is hepatic VLDL overproduction since PCSK9 mediates both apoB-100 and TG synthesis and VLDL assembly pathways [126,127]. In accordance, circulating PCSK9 levels were significantly correlated with serum TG levels in population studies [118,119]. Although there is a rationale for supporting the hypothesis that PCSK9 is involved in HDL metabolism [128], available data showed that PCSK9 is not associated with HDL-C level in obese subjects [110,111,122]. Similarly, little is known about the association between PCSK9 and sdLDL particles in obesity [129]. Several reasons could explain observed unexpected correlations or even lack of associations between plasma PCSK9, obesity indices and lipid profile in clinical and epidemiological studies. It is possible that that the effects observed *in vitro* or in experimental models might not translate into the same associations between plasma lipids and PCSK9 in human studies. Also, conclusions from studies with animal models should be carefully interpreted and translated taking into account the differences in lipoprotein metabolism between the species. Plasma concentration of PCSK9 has very high inter-individual variation [119]. Furthermore, PCSK9 circulates in plasma as intact and as an inactive, furin-cleaved form [130]. As already mentioned, approximately one third of plasma PCSK9 molecules are bound to LDL particles, having diminished activity toward LDL receptors [104]. Thus, it questionable whether plasma PCSK9 level reliable reflects its activity. Available methods do not distinguish between various PCSK9 forms, but measure its total plasma concentration. Development of the tests that quantify PCSK9 forms and/or PCSK9 activity would enable further insight into role of PCSK9 in metabolic dyslipidemia.

4.2. Sphingosine-1-phosphate in obesity

S1P is a member of the sphingolipid family, which comprises a large group of bioactive molecules with a wide range of physiological functions. Sphingolipids are produced in human body either by *de novo* synthesis or by the salvage pathways. S1P in circulation mainly originates from erythrocytes, platelets and endothelial cells [131–133]. The majority of S1P in plasma is bound to HDL particles, and the rest to albumin and other plasma lipoproteins [134]. Physiological effects of S1P are exerted through its interaction with the receptors on target cells, but also through its relationship with its carriers, principally HDL (Fig. 3).

S1P serves as a ligand for 5 different G protein-coupled receptors (S1PR1-5). In general, S1P promotes cell survival, mobility, proliferation, and differentiation, but tissue distribution of the receptors, as well as S1P coupling with specific G proteins ultimately determine its biological effects [136]. In line with this, Hashimoto et al. [137] reported that increased expression of S1P-producing enzyme sphingosine kinase is involved in the promotion of adipogenesis. More recently, it has been demonstrated that S1P stimulates proliferation of adipocytes and adipogenesis [138]. In contrast, Moon et al. [139] reported anti-adipogenic effects of S1P, but these effects are mediated only through S1PR2. Also, it has been demonstrated that the blockade of S1PR2 provokes adipocytes proliferation, but suppresses the differentiation of pre-adipocytes, whereas the opposite is true for S1PR1 [140]. Apart from the receptor-mediated signal pathways, S1P acts as an intracellular signal molecule by mediating TNF-α/NF-κB signalling pathway [141]. Taken altogether, the interplay of receptors' activation and deactivation determines the final effect of S1P, which might provide a ground for the future therapeutic use of S1P analogues.

Approximately two thirds of S1P in circulation is bound to HDL particles. Therefore, the interplay of S1P with serum lipids is predominantly related to the structure and function of HDL. A carrier of S1P within HDL particles is apolipoprotein M (apoM) [142]. This apolipoprotein contributes to atheroprotective effects of HDL by enhancing the cholesterol efflux and antioxidative properties of HDL, but also by serving as a S1P chaperone. Accumulating evidence implicates that atheroprotective actions of HDL strongly depend on the presence of S1P, as well as that the effects of S1P are mediated by its associations with HDL particles. In a recent study, Ruiz et al. [143] have demonstrated that the ability of HDL to act anti-apoptotically depends on the presence of S1P and apoM. On the other hand, anti-apoptotic effects of S1P were more prominent in complex with apoM and HDL, compared to free S1P or its complex with albumin [143]. Similar findings were reported regarding anti-inflammatory and vasodilatatory properties of the S1P [144–146].

It has been demonstrated that obesity influences the entire sphingolipid metabolism. The researchers have found an increased amount of multiple sphingolipids, including S1P in adipocytes of obese individuals [147]. In addition, plasma levels of S1P in obese mice, as well as in obese humans were reported to be elevated [148]. Still, Majumdar et al. [149] found no differences in S1P levels of overweight and lean adolescents. More recent studies shed new light on the relationship between obesity and S1P. Namely, by analysing the liver metabolome, Green et al. [150] demonstrated that calorie restriction causes significant alterations of ceramide and S1P signalling pathways in mice. The authors reported a significantly increased expression of liver S1P, as a response to graded calorie restriction. In addition, S1P negatively correlated with decreasing body mass [150]. Conversely, Silva et al. [151] have found an increase in circulating S1P levels following a high-fat diet in rats. Nonetheless, the same authors [151] demonstrated that a high-fat diet caused a downregulation of hypothalamic S1PR1 protein levels and consequent dysregulation of S1P/S1PR interaction in the neurons of hypothalamus, which is crucial for control of energy balance. Another interesting finding was recently reported by Christoffersen et al. [152]. Namely, the authors showed that apoM$^{-/-}$ mice lacking of S1P signalization have enlarged and hyperactive brown adipose tissue with enhanced TG utilization. Based on these findings, a hypothesis has been raised according to which apoM-S1P complex might have evolutional role in preventing detrimental effects of starvation, but in the condition of food excess, these bioactive molecules might contribute to the obesity development [153].

Green et al. [150] reported negative correlation of liver S1P with circulating leptin levels. Also, it has been shown that leptin resistance in obese rats is associated with increased plasma S1P levels, probably as a compensatory effect [151]. Previously, Holland et al. [154] demonstrated that adiponectin stimulates production of S1P, through activation of both adiponectin receptors AdipoR1/2 and subsequent enhancing of ceramidase activity. More recently, Choi et al. [155] confirmed these findings by demonstrating a decrease in ceramide and increase of S1P following administration of an adiponectin receptor agonist. Thus, accumulating evidences suggest an intrinsic connection between adipokines and sphingolipid metabolism, with S1P as one of the prominent features inside of this metabolic loop. It is noteworthy that, in contrast with numerous investigations on cell cultures and animal models, a number of studies analysing S1P plasma levels in obese or overweight human subjects is relatively small. However, it is clear that the affinity of S1P towards different receptors, but also towards different carriers, determines its final effect in the body. HDL, as the main carrier of S1P in plasma, enables beneficiary effects of this signalling molecule.

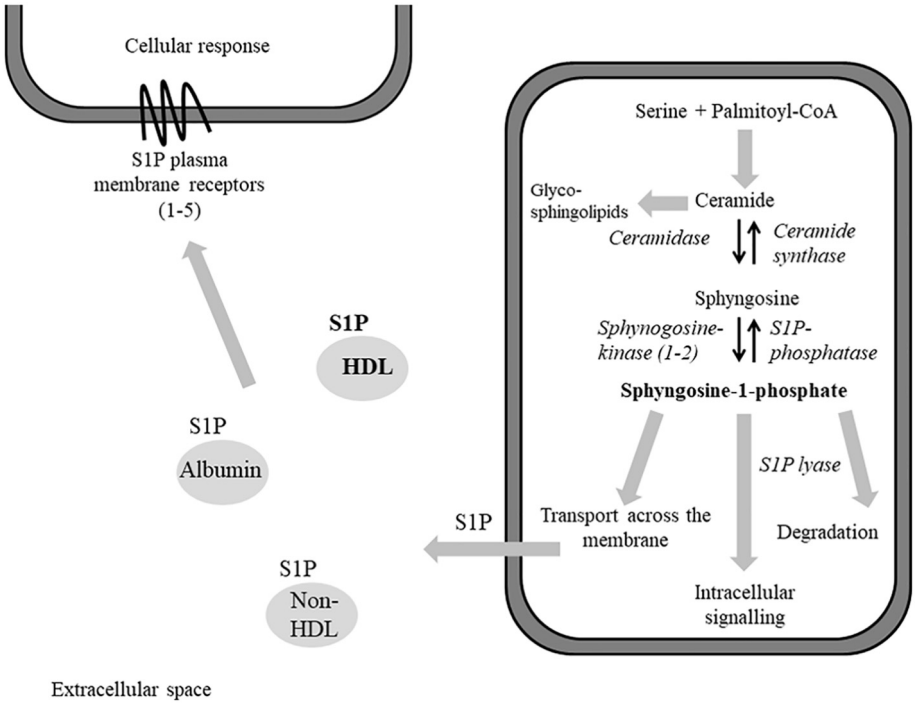

Fig. 3. Metabolism and plasma distribution of S1P. De novo synthesis of S1P starts with a condensation of serine and palmitoyl-CoA and leads to the formation of the major precursor of the entire sphingolipid network: ceramide. Through the activities of several enzymes (sphingomyelin synthase, glucosyl-ceramide synthase or galactosyl-ceramide synthase), ceramide is transformed into sphingomyelin, glucosyl-ceramide, galactosyl-ceramide and further into various glycosphingolipids. In a distinct metabolic pathway ceramide is, by the activities of five different ceramidases, deacylated and transformed into sphingosine. Sphingosine kinases 1 and 2 catalyse the phosphorylation of sphyngosine and formation of S1P. Further metabolism of S1P goes either back to sphingosine throughout the dephosphorisation, or towards an irreversible exit from the sphingolipid metabolism pathway, throughout the cleavage by the activity of S1P lyase [135]. S1P participates in intracellular signalling, or is transported to extracellular space, wherein it bounds to HDL, albumin, or other lipoproteins. Physiological effects of extracellular S1P are accomplished through the associations with membrane S1P receptors (1-5). S1P, sphingosine-1-phosphate; HDL, high-density lipoprotein.

In addition, one should not neglect that obesity is linked with attenuated HDL production and compromised HDL function. In such conditions, higher proportion on S1P will be attached to alternative chaperones, resulting in attenuated or even reversed effects of S1P. In confirming such hypothesis, recently it was reported that apoM-S1P complex is shifted from dense to light HDL particles in women with type 1 diabetes, whereby such assembly of apoM-S1P and light HDL particles is less efficient in promoting anti-inflammatory activities [156].

4.3. Circulating miRNA as biomarkers of dyslipidemia in obesity

Circulating miRNAs are recently established as biomarkers for several diseases and have been repeatedly studied in the context of CVD pathogenesis [157]. Although studies identified numerous miRNAs with important roles in regulation of lipid metabolism [158], a special emphasis will be placed on mir-33a and mir-33b, since they are involved in the regulation of cholesterol and fatty acid metabolism and insulin signalling, which are the hallmarks of metabolic dyslipidemia.

Due to the presence of mir-33a and mir-33b in the introns of the genes encoding transcription factors SREBP1 and SREBP2, respectively, the induction of SREBPs will also induce microRNAs expression. As a consequence, mir-33a upregulation will increase cholesterol synthesis and uptake (via SREBP1-mediated activation of *HMGCR* and *LDLR* genes), and reduce cholesterol efflux (by targeting *ABCA1* and *ABCG1* genes) and elimination (by targeting *CYP7A1* gene) [158]. Similarly, activation of mir-33b will increase cellular lipids, by targeting the genes controlling fatty acid synthesis and oxidation, and also reduce insulin signal transduction, by suppression of IRS-2 gene expression [159]. While the functional roles of mir-33a and mir-33b have been highly investigated, studies on their circulating levels as potential biomarkers are underway. Martino and colleagues [160] found increased plasma miR-33a and miR-33b levels in hypercholesterolemic children and suggested their use as early biomarkers of disrupted cholesterol homeostasis in childhood. In a recent study, both circulating miR-33a and miR-33b levels were positively associated with the levels of serum TC and LDL-C in type 2 diabetes patients with high CVD risk [161]. Finally, miRNA profile analysis in plasma of CVD patients showed three times higher expression of miRNA-33 than in controls [162].

Bonding to HDL and LDL particles protects circulating miRNAs from degradation by RNAses, while, in turn, miRNA cargo of HDL and LDL particles controls their function [158]. Based on the findings that miRNA profile of HDL in healthy subjects differs from the profile in patients with familiar hypercholesterolemia [163] and acute coronary syndrome [164], a hypothesis of unique HDL-associated miRNA footprint in health and diseases has been raised. Subsequent investigations revealed that miR-223, the most abundant miRNA in HDL, mediates HDL anti-inflammatory function [165]. Of note, LDL particles also carry certain amount of miRNA-223, but its role in LDL metabolism is less understood, as compared to miR-155, the most abundant miRNA in LDL, which has pro-atherogenic properties [166]. Recent studies showed that both circulating miR-223 [167] and miR-155 [168] levels correlate with severity of coronary atherosclerosis. Further improvements of the methods for detection of miRNAs in HDL and LDL particles will enable answering the question whether lipoprotein-associated miRNAs may serve as early and sensitive biomarkers of dyslipidemia [169].

5. Implications for cardiovascular disease prevention

Despite significant preventive and therapeutic efforts, development of CVD remains the principal unfavourable outcome of obesity. With an aim to reduce the overall risk for cardiovascular and other chronic complications, clinical practice guidelines for management of obesity acknowledge that the treatment of co-morbidities should be integral part of the obese patients' care [170]. Specific guidelines for the treatment of dyslipidemia in obesity are recently released by the European Society of Hypertension and European Association for the Study of

Obesity [171]. These guidelines recommend lifestyle modification for weight reduction as the main strategy for the regulation of lipid profile [171]. Although obese patients usually have elevated TG and low HDL-C levels, the primary goal of dyslipidemia management is the reduction of LDL-C levels. Actual European guidelines for management of dyslipidemia recognise patients with metabolic syndrome as high-risk individuals and recommend lipid-lowering therapy for those with elevated LDL-C [172], which is applicable to subjects with MUO [71]. Will the newest American College of Cardiology/American Heart Association (AHA) cholesterol guidelines provide specific recommendations for obese patients remain to be seen upon their release in AHA Scientific Sessions 2018 [173].

Apart from well-known strategies aimed to control traditional lipid parameters, contemporary research revealed a range of new modulators of obesity and dyslipidemia, thus providing possibilities for new approaches in prevention of these conditions and related complications. The recognition of MHO and MUO phenotypes might represent the first step in this direction. It is clear that the maintenance of healthy weight depends on a delicate balance between individual susceptibility and lifestyle habits. Although the recognition of MHO phenotype changed the perspective of cardiometabolic risk in obesity, several prospective studies reported transition from MHO to MUO phenotype during follow-up [71,77]. This finding completely fits the conclusion that MHO should be considered as a transient state rather than as a permanent phenotype with low risk [71]. Therefore, additional efforts should be conferred to maintaining MHO phenotype by dietary interventions and overall changes of lifestyle.

An emerging topic of modern scientific investigations is whether novel markers of dyslipidemia are also susceptible to non-pharmacological interventions. To date, several studies have investigated the effects of weight loss on plasma PCSK9 levels in obese subjects. In the study of Filippatos et al. [109] no significant change of PCSK9 level was found after three months of the low-fat dietary intervention program, despite significant weight loss. Similarly, a one-year lifestyle modification program in the study of 117 abdominally obese men showed modest effects on plasma PCSK9 level reduction [129]. Dietary patterns and interventions have different effects on plasma PCSK9 level: it was unchanged following short-term high-fat or high-fat/high-protein diet, increased after high-fructose diet [117] and reduced by Mediterranean diet [174]. As it has been mentioned above, dietary restrictions can increase levels of S1P and expression of S1P receptors [150]. Since S1P associated with HDL particles exhibits significant anti-atherogenic properties, elevation of S1P might present another favourable aspect included in atheroprotective actions of restrictive diet and weight loss. It is also interesting to mention possible effects of physical activity on S1P. Namely, it has been demonstrated that physical exercise increases levels of S1P in animal models [151]. In addition, recent investigation demonstrated selective increase of HDL-associated S1P after the endurance training [175]. Such novel findings implicate that well-known atheroprotective modulators, like restrictive diet and exercise, might have additional beneficial effects which offers new possibilities for preventive actions.

Although many pieces of evidence have pointed toward strong associations of vitamin D deficiency with dyslipidemia, the majority of intervention trials failed to prove beneficial effects of vitamin D supplementation [58], so the question of vitamin D treatment in obese individuals and dyslipidemic patients still remains open. Also, it is noteworthy that, to the best of our knowledge, all previous researches focused on quantitative, but not on qualitative changes of serum lipoproteins. Future studies should elucidate whether vitamin D has any effect on quality and functionality of lipoprotein particles.

6. Conclusion

Impaired production of adipokines and chronic low-grade inflammation in adipose tissue form the base for insulin resistance, which is the main driving force in the development of metabolic dyslipidemia in obesity. In addition, numerous epidemiological data linked vitamin D deficiency and metabolic dyslipidemia, although a clear demonstration of causal relationship is still lacking. The concept of MHO has been recently recognised, indicating a transitional state of relative protection against obesity-related metabolic complications. Knowing that dyslipidemia has a polygenic background, which is additionally modified by the interactions with various epigenetic and environmental factors, this phenomenon may have important implication for long-term cardiovascular prevention in MHO and deserves additional attention. Finally, further investigations of novel lipid biomarkers in obesity would potentially yield new therapeutic approaches for controlling metabolic dyslipidemia and cardiometabolic risk in obesity.

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Author contribution

All authors equally contributed to the present work.

Declarations of interest

None.

References

[1] Muir LA, Neeley CK, Meyer KA, Baker NA, Brosius AM, Washabaugh AR, et al. Adipose tissue fibrosis, hypertrophy, and hyperplasia: correlations with diabetes in human obesity. Obesity (Silver Spring) 2016;24:597–603.
[2] Castoldi A, Naffah de Souza C, Camara NO, Morraes-Vieira PM. The macrophage switch in obesity development. Front Immunol 2016;6:637.
[3] Blüher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Pract Res Clin Endocrinol Metab 2013;27:163–77.
[4] Klop B, Elte JWF, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. Nutrients 2013;5:1218–40.
[5] Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff Jr DC. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol 2011:105–13.
[6] Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation 2016;133:1104–14.
[7] Magkos F, Fabbrini E, Mohammed BS, Patterson BW, Klein S. Increased whole-body adiposity without a concomitant increase in liver fat is not associated with augment metabolic dysfunction. Obesity (Silver Spring) 2010;18:1510–5.
[8] Pagliassotti MJ, Kim PY, Estrada AL, Stewart CM, Gentile CL. Endoplasmic reticulum stress in obesity and obesity-related disorders: an expanded view. Metabolism 2016;65:1238–46.
[9] Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? Curr Opin Endocrinol Diabetes Obes 2012;19:81–7.
[10] Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in development of insulin resistance and β-cell dysfunction. Eur J Clin Investig 2002;32:14–23.
[11] Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract 2011;93(Suppl. 1):S52–9.
[12] Hass ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. Trends Endocrinol Metab 2013;24:391–7.
[13] Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. J Am Coll Cardiol 2010;55:1283–99.
[14] Capurso C, Capurso A. From excess adiposity to insulin resistance: the role of free fatty acids. Vasc Pharmacol 2012;57:91–7.
[15] Draznin B. Molecular mechanisms of insulin resistance: serine phosphorylation of insulin receptor substrate-1 and increased expression of p85alpha: the two sides of a coin. Diabetes 2006;55:2392–7.
[16] Ringseis R, Eder K, Mooren FC, Krüger K. Metabolic signals and innate immune activation in obesity and exercise. Exerc Immunol Rev 2015;21:58–68.
[17] Engin A. The pathogenesis of obesity-associated adipose tissue inflammation. Adv Exp Med Biol 2017;960:221–45.
[18] Lionetti L, Mollica MP, Lombardi A, Cavaliere G, Gifuni G, Barietta A. From chronic overnutrition to insulin resistance: the role of fat-storing capacity and inflammation. Nutr Metab Cardiovasc Dis 2009;9:146–52.
[19] Samuel VT, Shulman GI. The pathogenesis of insulin resistance: intergrating signaling pathways and substrate flux. J Clin Invest 2016;126:12–22.
[20] Petersen MC, Shulman GI. Mechanisms of insulin action and resistance. Physiol Rev 2018;98:2133–223.
[21] Knights AJ, Funnel APW, Pearsin RCM, Crossley M, Bell-Anderson KS. Adipokines and insulin action. Adipocyte 2014;3:88–96.

[22] Pessin JE, Kwon H. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 2013;4:71.
[23] Lönnqvist F. The obese (ob) gene and its product leptin—a new route toward obesity treatment in man? Q J Med 1996;89:327–32.
[24] Likuni N, Lam QLK, Lu L, Matarese G, La Cava A. Leptin and inflammation. Curr Immunol Rev 2008;4:70–9.
[25] Perry RJ, Petersen KF, Shulman GI. Pleotropic effects of leptin to reverse insulin resistance and diabetic ketoacidosis. Diabetologia 2016;59:933–7.
[26] Rashid S. Mechanisms by which elevated resistin levels accelerate atherosclerotic cardiovascular disease. Rheumatol Curr Res 2013;115.
[27] Chen X, Xun K, Chen L, Wang Y. TNF-alpha, a potent lipid metabolism regulator. Cell Biochem Funct 2009;27:407–16.
[28] Leguisamo NM, Lehnen AM, Machado UF, Okamtoto MM, Markosi MM, Pinto GH, et al. GLUT4 content decreases along with insulin resistance and high levels of inflammatory markers in rats with metabolic syndrome. Cardiovasc Diabetol 2012;11:100.
[29] Rui L, Aguirre V, Kim JK, Shulman GI, Lee A, Corbould A, et al. Insulin/IGF-1 and TNF-α stimulate phosphorylation of IRS-1 at inhibitory Ser^{307} via distinct pathways. J Clin Invest 2001;107:181–9.
[30] Weigert C, Hoene M. The role of interleukin-6 in insulin resistance, body fat distribution and energy balance. Obes Rev 2008;9:20–9.
[31] Matsuki T, Horai R, Sudo K, Iwakura Y. IL-1 plays an important role in lipid metabolism by regulating insulin levels under physiological conditions. J Exp Med 2003; 198:877–88.
[32] Baker RG, Hayden MS, Ghosh S. NF-Kb, inflammation and metabolic disease. Cell Metab 2011;13:11–22.
[33] Rhman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how they are interlinked? J Biomed Sci 2016;23:87.
[34] Han X, Kitamoto S, Lian Q, Boisvert WA. Interleukin-10 facilitates both cholesterol uptake and efflux in macrophages. J Biol Chem 2009;284:32950–8.
[35] Schindler M, Pendzialek M, Grybel KJ, Seeling T, Gurke J, Fischer B, et al. Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocysts. Hum Reprod 2017;32:1382–92.
[36] Lesná J, Tichá A, Hyšpler R, Musil F, Bláha V, Sobotka L, et al. Omentin-1 plasma levels and cholesterol metabolism in obese patients with diabetes mellitus type 1: impact of weight reduction. Nutr Diabetes 2015;5:e183.
[37] Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev 2005;6:13–21.
[38] Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia 2012;55:2319–26.
[39] Izadi V, Farabad E, Azadbakht L. Epidemiologic evidence on serum adiponectin level and lipid profile. Int J Prev Med 2013;4:133–40.
[40] Qiao L, Zou C, van der Westhuyzen DR, Shao J. Adiponectin reduces plasma triglyceride by increasing VLDL triglyceride catabolism. Diabetes 2008;57:1824–33.
[41] Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. J Biol Chem 2010;285:6153–60.
[42] Carstensen M, Herder C, Kempf K, Erlund I, Martin S, Koenig W, et al. Sfrp5 correlates with insulin resistance and oxidative stress. Eur J Clin Investig 2013;43:350–7.
[43] Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R, et al. Sfrp5 Is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. Science 2010;329:454–7.
[44] Hu Z, Deng H, Qu H. Plasma SFRP5 levels are decreased in Chinese subjects with obesity and type 2 diabetes and negatively correlated with parameters of insulin resistance. Diabetes Res Clin Pract 2013;99:391–5.
[45] Carstensen-Kirberg M, Kannenberg JM, Huth C, Meisinger C, Koenig W, Heier M, et al. Invesre association between serum levels of secreted frizzled–related protein-5 (SFRP5) and multiple cardiometabolic risk factors: KORA F4 study. Cardiovasc Diabetol 2017;16:109.
[46] Abbas MA. Physiological functions of vitamin D in adipose tissue. J Steroid Biochem Mol Biol 2017;165:369–81.
[47] Marcotorchino J, Gouranton E, Romier B, Tourniaire F, Astier J, Malezet C, et al. Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. Mol Nutr Food Res 2012;56:1771–82.
[48] Ding C, Gao D, Wilding J, Trayhurn P, Bing C. Vitamin D signalling in adipose tissue. Br J Nutr 2012;108:1915–23.
[49] Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, Donadel G, et al. Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med 2013;8:33–40.
[50] Stokic E, Kupusinac A, Tomic-Naglic D, Smiljenic D, Kovacev-Zavisic B, Srdic-Galic B, et al. Vitamin D and dysfunctional adipose tissue in obesity. Angiology 2015;66: 613–8.
[51] Sergeev IN. 1,25-Dihydroxyvitamin D3 induces Ca^{2+}-mediated apoptosis in adipocytes via activation of calpain and caspase-12. Biochem Biophys Res Commun 2009;384:18–21.
[52] Ching S, Kashinkunti S, Niehaus MD, Zinser GM. Mammary adipocytes bioactivate 25-hydroxyvitamin D_3 and signal via vitamin D_3 receptor, modulating mammary epithelial cell growth. J Cell Biochem 2011;112:3393–405.
[53] Nimitphong H, Holick MF, Fried SK, Lee MJ. 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 promote the differentiation of human subcutaneous preadipocytes. PLoS One 2012;7:e52171.
[54] Jorde R, Figenschau Y, Hutchinson M, Emaus N, Grimnes G. High serum 25-hydroxyvitamin D concentrations are associated with a favorable serum lipid profile. Eur J Clin Nutr 2010;64:1457–64.
[55] Lupton JR, Faridi KF, Martin SS, Sharma S, Kulkarni K, Jones SR, et al. Deficient serum 25-hydroxyvitamin D is associated with an atherogenic lipid profile: The Very Large Database of Lipids (VLDL-3) study. J Clin Lipidol 2016;10:72–81.e1.
[56] Ooi EM, Afzal S, Nordestgaard BG. Elevated remnant cholesterol in 25-hydroxyvitamin D deficiency in the general population: Mendelian randomization study. Circ Cardiovasc Genet 2014;7:650–8.
[57] Vitezova A, Voortman T, Zillikens MC, Jansen PW, Hofman A, Uitterlinden AG, et al. Bidirectional associations between circulating vitamin D and cholesterol levels: The Rotterdam Study. Maturitas 2015;82:411–7.
[58] Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. Prog Lipid Res 2011;50:303–12.
[59] Pérez-Castrillón JL, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, et al. Effects of Atorvastatin on vitamin D levels in patients with acute ischemic heart disease. Am J Cardiol 2007;99:903–5.
[60] Ertugrul DT, Yavuz B, Cil H, Ata N, Akin KO, Kucukazman M, et al. STATIN-D study: comparison of the influences of rosuvastatin and fluvastatin treatment on the levels of 25 hydroxyvitamin D. Cardiovasc Ther 2011;29:146–52.
[61] Glossmann HH, Blumthaler M. Does rosuvastatin increase serum levels of 25-hydroxy-vitamin D? Dermatoendocrinol 2012;4:2–7.
[62] Anagnostis P, Adamidou E, Slavakis A, Polyzos SA, Selalmatzidou D, Panagiotou A, et al. Comparative effect of atorvastatin and rosuvastatin on 25-hydroxy-vitamin D levels in non-diabetic patients with dyslipidaemia: A prospective randomized open-label pilot study. Open Cardiovasc Med J 2014;8:55–60.
[63] Chow EC, Magomedova L, Quach HP, Patel R, Durk MR, Fan J, et al. Vitamin D receptor activation down-regulates the small heterodimer partner and increases CYP7A1 to lower cholesterol. Gastroenterology 2014;146:1048–59.
[64] Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, Saris WH, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. Obes Rev 2009;10:475–86.
[65] Boon N, Hul GB, Stegen JH, Sluijsmans WE, Valle C, Langin D, et al. An intervention study of the effects of calcium intake on faecal fat excretion, energy metabolism and adipose tissue mRNA expression of lipid-metabolism related proteins. Int J Obes 2007;31:1704–12.
[66] Kjølbæk L, Lorenzen JK, Larsen LH, Astrup A. Calcium intake and the associations with faecal fat and energy excretion, and lipid profile in a free-living population. J Nutr Sci 2017;6:e50.
[67] Liang K, Oveisi F, Vaziri ND. Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. Kidney Int 1998;53:626–30.
[68] Vaziri ND, Liang K. Role of secondary hyperparathyroidism in the pathogenesis of depressed lipoprotein lipase expression in chronic renal failure. Am J Phys 1997; 273:F925–30.
[69] Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: understanding metabolically unhealthy normal weight or metabolically healthy obese patients. Metabolism 2016;65:73–80.
[70] Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300.
[71] Blüher M. Are metabolically healthy obese individuals really healthy? Eur J Endocrinol 2014;171:R209–19.
[72] Song Y, Manson JE, Meigs JB, Ridker PM, Buring JE, Liu S. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. Am J Cardiol 2007;100:1654–8.
[73] Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. Ann Intern Med 2013;159:758–69.
[74] Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 2016;23:956–66.
[75] Schröder H, Ramos R, Baena-Díez JM, Mendez MA, Canal DJ, Fíto M, et al. Determinants of the transition from a cardiometabolic normal to abnormal overweight/obese phenotype in a Spanish population. Eur J Nutr 2014;53:1345–53.
[76] Phillips CM, Perry IJ. Lipoprotein particle subclass profiles among metabolically healthy and unhealthy obese and non-obese adults: does size matter? Atherosclerosis 2015;242:399–406.
[77] Hansen L, Netterstrøm MK, Johansen NB, Rønn PF, Vistisen D, Husemoen LLN, et al. Metabolically healthy obesity and ischemic heart disease: a 10-year follow-up of the Inter99 study. J Clin Endocrinol Metab 2017;102:1934–42.
[78] Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Small, dense low-density lipoprotein and C-reactive protein in obese subjects with and without other criteria for the metabolic syndrome. J Clin Lipidol 2007;1:599–604.
[79] Kim S, Lee H, Lee DC, Lee HS, Lee JW. Predominance of small dense LDL differentiates metabolically unhealthy from metabolically healthy overweight adults in Korea. Metabolism 2014;63:415–21.
[80] Jensen MK, Chiuve SE, Rimm EB, Dethlefsen C, Tjønneland A, Joensen AM, et al. Obesity, behavioral lifestyle factors, and risk of acute coronary events. Circulation 2008;117:3062–9.
[81] Sung KC, Lee MY, Kim YH, Huh JH, Kim JY, Wilde SH, et al. Obesity and incidence of diabetes: effect of absence of metabolic syndrome, insulin resistance, inflammation and fatty liver. Atherosclerosis 2018;275:50–7.
[82] Janghorbani M, Salamat MR, Amini M, Aminorroaya A. Risk of diabetes according to the metabolic health status and degree of obesity. Diabetes Metab Syndr 2017;1: S439–44.
[83] Ipsen DH, Tveden-Nyborg P, Lykkesfeldt J. Dyslipidemia: obese or not obese-that is not the question. Curr Obes Rep 2016;5:405–12.
[84] Gonçalves CG, Glade MJ, Meguid MM. Metabolically healthy obese individuals: key protective factors. Nutrition 2016;32:14–20.
[85] Zachariah JP, Quiroz R, Nelson KP, Teng Z, Keaney JF, Sullivan LM, et al. Prospective relation of circulating adipokines to incident metabolic syndrome: The Framingham Heart Study. J Am Heart Assoc 2017;6:e004974.

[86] Ahl S, Guenther M, Zhao S, James R, Marks J, Szabo A, et al. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. J Clin Endocrinol Metab 2015;100:4172–80.
[87] Chang CS, Lu YJ, Chang HH, Hsu SH, Kuo PH, Shieh CC, et al. Role of adiponectin gene variants, adipokines and hydrometry-based percent body fat in metabolically healthy and abnormal obesity. Obes Res Clin Pract 2018;12:49–61.
[88] Eglit T, Ringmets I, Lember M. Obesity, high-molecular-weight (HMW) adiponectin, and metabolic risk factors: prevalence and gender-specific associations in Estonia. PLoS One 2013;8:e73273.
[89] Morrison JA, Glueck CJ, Daniels S, Wang P, Horn P, Stroop D. Paradoxically high adiponectin and the healthy obese phenotype in obese black and white 16 year old girls. Transl Res 2010;156:302–8.
[90] Morrison JA, Glueck CJ, Daniels S, Wang P, Stroop D. Paradoxically high adiponectin in obese 16-year-old girls protects against appearance of the metabolic syndrome and its components seven years later. J Pediatr 2011;158:208–14.
[91] Muñoz-Garach A, Cornejo-Pareja I, Tinahones FJ. Does metabolically healthy obesity exist? Nutrients 2016;8:OE07–10.
[92] Jones Buie JN, Goodwin AJ, Cook JA, Halushka PV, Fan H. The role of miRNAs in cardiovascular disease risk factors. Atherosclerosis 2016;254:271–81.
[93] Abente EJ, Subramanian M, Ramachandran V, Najafi-Shoushtari SH. MicroRNAs in obesity-associated disorders. Arch Biochem Biophys 2016;589:108–19.
[94] Yaribeygi H, Katsiki N, Behnam B, Iranpanah H, Sahebkar A. MicroRNAs and type 2 diabetes mellitus: molecular mechanisms and the effect of antidiabetic drug treatment. Metabolism 2018;87:48–55.
[95] Ortega FJ, Moreno-Navarrete JM, Pardo G, Sabater M, Hummel M, Ferrer A, et al. miRNA expression profile of human subcutaneous adipose and during adipocyte differentiation. PLoS One 2010;5:e9022.
[96] Ortega FJ, Mercader JM, Catalan V, Moreno-Navarrete JM, Pueyo N, Sabater M, et al. Targeting the circulating microRNA signature of obesity. Clin Chem 2013;59:781–92.
[97] Cui X, You L, Zhu L, Wang X, Zhou Y, Li Y, et al. Change in circulating microRNA profile of obese children indicates future risk of adult diabetes. Metabolism 2018;78:95–105.
[98] Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci 2007;32:71–7.
[99] Gustafsen C, Olsen D, Vilstrup J, Lund S, Reinhardt A, Wellner N, et al. Heparan sulfate proteoglycans present PCSK9 to the LDL receptor. Nat Commun 2017;8:503.
[100] Lagace TA. PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells. Curr Opin Lipidol 2014;25:387–93.
[101] Reiss AB, Shah N, Muhieddine D, Zhen J, Yudkevich J, Kasselman LJ, et al. PCSK9 in cholesterol metabolism: from bench to bedside. Clin Sci (Lond) 2018;132:1135–53.
[102] Poirier S, Mayer G, Poupon V, McPherson PS, Desjardins R, Ly K, et al. Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation: evidence for an intracellular route. J Biol Chem 2009;284:28856–64.
[103] Jeong HJ, Lee HS, Kim KS, Kim YK, Yoon D, Park SW. Sterol-dependent regulation of proprotein convertase subtilisin/kexin type 9 expression by sterol-regulatory element binding protein-2. J Lipid Res 2008;49:399–409.
[104] Kosenko T, Golder M, Leblond G, Weng W, Lagace TA. Low density lipoprotein binds to proprotein convertase subtilisin/kexin type-9 (PCSK9) in human plasma and inhibits PCSK9-mediated low density lipoprotein receptor degradation. J Biol Chem 2013;288:8279–88.
[105] Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. N Engl J Med 2016;375:2144–53.
[106] Glerup S, Schulz R, Laufs U, Schlüter KD. Physiological and therapeutic regulation of PCSK9 activity in cardiovascular disease. Basic Res Cardiol 2017;112:32.
[107] Katsiki N, Athyros VG, Mikhailidis DP, Mantzoros C. Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors: shaping the future after the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trial. Metabolism 2017;74:43–6.
[108] Tóth Š, Fedačko J, Pekárová T, Hertelyová Z, Katz M, Mughees A, et al. Elevated circulating PCSK9 concentrations predict subclinical atherosclerotic changes in low risk obese and non-obese patients. Cardiol Ther 2017;6:281–9.
[109] Filippatos TD, Liberopoulos E, Georgoula M, Tellis CC, Tselepis AD, Elisaf M. Effects of increased body weight and short-term weight loss on serum PCSK9 levels - a prospective pilot study. Arch Med Sci Atheroscler Dis 2017;2:e46–51.
[110] Levenson AE, Shah AS, Khoury PR, Kimball TR, Urbina EM, de Ferranti SD, et al. Obesity and type 2 diabetes are associated with elevated PCSK9 levels in young women. Pediatr Diabetes 2017;18:755–60.
[111] Hasan H, Attlee A, Raigangar V, Madkour M, Awadallah S. Proprotein convertase subtilisin/kexin type 9 (PCSK9) and metabolic syndrome components among young adult females. Diabetes Metab Syndr 2017;11:S337–41.
[112] Chan DC, Pang J, McQuillan BM, Hung J, Beilby JP, Barrett PHR, et al. Plasma proprotein convertase subtilisin kexin type 9 as a predictor of carotid atherosclerosis in asymptomatic adults. Heart Lung Circ 2016;25:520–5.
[113] Miao J, Manthena PV, Haas ME, Ling AV, Shin DJ, Graham MJ, et al. Role of insulin in the regulation of proprotein convertase subtilisin/kexin type 9. Arterioscler Thromb Vasc Biol 2015;35:1589–96.
[114] Costet P, Cariou B, Lambert G, Lalanne F, Lardeux B, Jarnoux AL, et al. Hepatic PCSK9 expression is regulated by nutritional status via insulin and sterol regulatory element-binding protein 1c. J Biol Chem 2006;281:6211–8.
[115] Kappelle PJ, Lambert G, Dullaart RP. Plasma proprotein convertase subtilisin-kexin type 9 does not change during 24h insulin infusion in healthy subjects and type 2 diabetic patients. Atherosclerosis 2011;214:432–5.
[116] Awan Z, Dubuc G, Faraj M, Dufour R, Seidah NG, Davignon J, et al. The effect of insulin on circulating PCSK9 in postmenopausal obese women. Clin Biochem 2014;47:1033–9.
[117] Cariou B, Langhi C, Le Bras M, Bortolotti M, Lê KA, Theytaz F, et al. Plasma PCSK9 concentrations during an oral fat load and after short term high-fat, high-fat high-protein and high-fructose diets. Nutr Metab (Lond) 2013;10:4.
[118] Baass A, Dubuc G, Tremblay M, Delvin EE, O'Loughlin J, Levy E, et al. Plasma PCSK9 is associated with age, sex, and multiple metabolic markers in a population-based sample of children and adolescents. Clin Chem 2009;55:1637–45.
[119] Lakoski SG, Lagace TA, Cohen JC, Horton JD, Hobbs HH. Genetic and metabolic determinants of plasma PCSK9 levels. J Clin Endocrinol Metab 2009;94:2537–43.
[120] Hampton EN, Knuth MW, Li J, Harris JL, Lesley SA, Spraggon G. The self-inhibited structure of full-length PCSK9 at 1.9 A reveals structural homology with resistin within the C-terminal domain. Proc Natl Acad Sci U S A 2007;104:14604–9.
[121] Melone M, Wilsie L, Palyha O, Strack A, Rashid S. Discovery of a new role of human resistin in hepatocyte low-density lipoprotein receptor suppression mediated in part by proprotein convertase subtilisin/kexin type 9. J Am Coll Cardiol 2012;59:1697–705.
[122] Kwakernaak AJ, Lambert G, Dullaart RP. Relationship of proprotein convertase subtilisin-kexin type 9 levels with resistin in lean and obese subjects. Clin Biochem 2012;45:1522–4.
[123] Du Y, Li S, Cui CJ, Zhang Y, Yang SH, Li JJ. Leptin decreases the expression of low-density lipoprotein receptor via PCSK9 pathway: linking dyslipidemia with obesity. J Transl Med 2016;14:276.
[124] Levenson AE, Haas ME, Miao J, Brown RJ, de Ferranti SD, Muniyappa R, et al. Effect of leptin replacement on PCSK9 in ob/ob mice and female lipodystrophic patients. Endocrinology 2016;157:1421–9.
[125] Vatier C, Arnaud L, Prieur X, Guyomarch B, Le May C, Bigot E, et al. One-year metreleptin therapy decreases PCSK9 serum levels in diabetic patients with monogenic lipodystrophy syndromes. Diabetes Metab 2017;43:275–9.
[126] Rashid S, Tavori H, Brown PE, Linton MF, He J, Giunzioni I, et al. Proprotein convertase subtilisin kexin type 9 promotes intestinal overproduction of triglyceride-rich apolipoprotein B lipoproteins through both low-density lipoprotein receptor-dependent and -independent mechanisms. Circulation 2014;130:431–41.
[127] Sun H, Samarghandi A, Zhang N, Yao Z, Xiong M, Teng BB. Proprotein convertase subtilisin/kexin type 9 interacts with apolipoprotein B and prevents its intracellular degradation, irrespective of the low-density lipoprotein receptor. Arterioscler Thromb Vasc Biol 2012;32:1585–95.
[128] Ferri N, Corsini A, Macchi C, Magni P, Ruscica M. Proprotein convertase subtilisin kexin type 9 and high-density lipoprotein metabolism: experimental animal models and clinical evidence. Transl Res 2016;173:19–29.
[129] Arsenault BJ, Pelletier-Beaumont E, Alméras N, Tremblay A, Poirier P, Bergeron J, et al. PCSK9 levels in abdominally obese men: association with cardiometabolic risk profile and effects of a one-year lifestyle modification program. Atherosclerosis 2014;236:321–6.
[130] Norata GD, Tavori H, Pirillo A, Fazio S, Catapano AL. Biology of proprotein convertase subtilisin kexin 9: beyond low-density lipoprotein cholesterol lowering. Cardiovasc Res 2016;112:429–42.
[131] Pappu R, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y, et al. Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science 2007;316:295–8.
[132] Gazit SL, Mariko B, Thérond P, Decouture B, Xiong Y, Couty L, et al. Platelet and erythrocyte sources of S1P are redundant for vascular development and homeostasis, but both rendered essential after plasma S1P depletion in anaphylactic shock. Circ Res 2016;119:e110–26.
[133] Venkataraman K, Lee YM, Michaud J, Thangada S, Ai Y, Bonkovsky HL, et al. Vascular endothelium as a contributor of plasma sphingosine 1-phosphate. Circ Res 2008;102:669–76.
[134] Kurano M, Yatomi Y. Sphingosine 1-phosphate and atherosclerosis. J Atheroscler Thromb 2018;25:16–26.
[135] Chalfant CE, Spiegel S. Sphingosine 1-phosphate and ceramide 1-phosphate: expanding roles in cell signaling. J Cell Sci 2005;118:4605–12.
[136] Pyne S, Pyne NJ. Translational aspects of sphingosine 1-phosphate biology. Trends Mol Med 2011;17:463–72.
[137] Hashimoto T, Igarashi J, Kosaka H. Sphingosine kinase is induced in mouse 3T3-L1 cells and promotes adipogenesis. J Lipid Res 2009;50:602–10.
[138] Lee SY, Lee HY, Song JH, Kim GT, Jeon S, Song YJ, et al. Adipocyte-specific deficiency of de novo sphingolipid biosynthesis leads to lipodystrophy and insulin resistance. Diabetes 2017;66:2596–609.
[139] Moon MH, Jeong JK, Park SY. Activation of S1P2 receptor, a possible mechanism of inhibition of adipogenic differentiation by sphingosine 1-phosphate. Mol Med Rep 2015;11:1031–6.
[140] Kitada Y, Kajita K, Taguchi K, Mori I, Yamauchi M, Ikeda T, et al. Blockade of sphingosine 1-phosphate receptor 2 signaling attenuates high-fat diet-induced adipocyte hypertrophy and systemic glucose intolerance in mice. Endocrinology 2016;157:1839–51.
[141] Alvarez SE, Harikumar KB, Hait NC, Allegood J, Strub GM, Kim EY, et al. Sphingosine-1-phosphate is a missing cofactor for the E3 ubiquitin ligase TRAF2. Nature 2010;465:1084–8.
[142] Christoffersen C, Nielsen LB. Apolipoprotein M: bridging HDL and endothelial function. Curr Opin Lipidol 2013;24:295–300.
[143] Ruiz M, Okada H, Dahlbäck B. HDL-associated ApoM is anti-apoptotic by delivering sphingosine 1-phosphate to S1P1 & S1P3 receptors on vascular endothelium. Lipids Health Dis 2017;16:36.
[144] Ruiz M, Frej C, Holmér A, Guo LJ, Tran S, Dahlbäck B. High-density lipoprotein-associated apolipoprotein M limits endothelial inflammation by delivering sphingosine-1-phosphate to the sphingosine-1-phosphate receptor 1. Arterioscler Thromb Vasc Biol 2017;37:118–29.
[145] Galvani S, Sanson M, Blaho VA, Swendeman SL, Obinata H, Conger H, et al. HDL-bound sphingosine 1-phosphate acts as a biased agonist for the endothelial cell receptor S1P1 to limit vascular inflammation. Sci Signal 2015;8:ra79.

[146] Toth PP. Activation of intracellular signaling systems by high-density lipoproteins. J Clin Lipidol 2010;4:376–81.
[147] Blachnio-Zabielska AU, Koutsari C, Tchkonia T, Jensen MD. Sphingolipid content of human adipose tissue: relationship to adiponectin and insulin resistance. Obesity (Silver Spring) 2012;20:2341–7.
[148] Kowalski GM, Carey AL, Selathurai A, Kingwell BA, Bruce CR. Plasma sphingosine-1-phosphate is elevated in obesity. PLoS One 2013;8:e72449.
[149] Majumdar I, Mastrandrea LD. Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome. Endocrine 2012;41:442–9.
[150] Green CL, Mitchell SE, Derous D, Wang Y, Chen L, Han JJ, et al. The effects of graded levels of calorie restriction: IX. Global metabolomic screen reveals modulation of carnitines, sphingolipids and bile acids in the liver of C57BL/6 mice. Aging Cell 2017;16:529–40.
[151] Silva VR, Micheletti TO, Pimentel GD, Katashima CK, Lenhare L, Morari J, et al. Hypothalamic S1P/S1PR1 axis controls energy homeostasis. Nat Commun 2014;5:4859.
[152] Christoffersen C, Federspiel CK, Borup A, Christensen PM, Madsen AN, Heine M, et al. The apolipoprotein M/S1P axis controls triglyceride metabolism and brown fat activity. Cell Rep 2018;22:175–88.
[153] Dahlbäck B. Lean ApoM−/− mice with hyperactive brown adipose tissue. Trends Endocrinol Metab 2018;29:283–4.
[154] Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 2011;17:55–63.
[155] Choi SR, Lim JH, Kim MY, Kim EN, Kim Y, Choi BS, et al. Adiponectin receptor agonist AdipoRon decreased ceramide, and lipotoxicity, and ameliorated diabetic nephropathy. Metabolism 2018;85:348–60.
[156] Frej C, Mendez AJ, Ruiz M, Castillo M, Hughes TA, Dahlbäck B, et al. A shift in ApoM/S1P between HDL-particles in women with type 1 diabetes mellitus is associated with impaired anti-inflammatory effects of the ApoM/S1P complex. Arterioscler Thromb Vasc Biol 2017;37:1194–205.
[157] Ultimo S, Zauli G, Martelli AM, Vitale M, McCubrey JA, Capitani S, et al. Cardiovascular disease-related miRNAs expression: potential role as biomarkers and effects of training exercise. Oncotarget 2018;9:17238–54.
[158] Desgagné V, Bouchard L, Guérin R. microRNAs in lipoprotein and lipid metabolism: from biological function to clinical application. Clin Chem Lab Med 2017;55:667–86.
[159] Dávalos A, Goedeke L, Smibert P, Ramírez CM, Warrier NP, Andreo U, et al. miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A 2011;108:9232–7.
[160] Martino F, Carlomosti F, Avitabile D, Persico L, Picozza M, Barillà F, et al. Circulating miR-33a and miR-33b are up-regulated in familial hypercholesterolaemia in paediatric age. Clin Sci (Lond) 2015;129:963–72.
[161] Deng X, Qin S, Chen Y, Liu HY, Yuan E, Deng H, et al. B-RCA revealed circulating miR-33a/b associates with serum cholesterol in type 2 diabetes patients at high risk of ASCVD. Diabetes Res Clin Pract 2018;140:191–9.
[162] Reddy LL, Shah SA, Ponde CK, Rajani RM, Ashavaid TF. Circulating miRNA-33: a potential biomarker in patients with coronary artery disease (CAD). Biomarkers 2018:1–27.
[163] Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011;13:423–33.
[164] Wagner J, Riwanto M, Besler C, Knau A, Fichtlscherer S, Röxe T, et al. Characterization of levels and cellular transfer of circulating lipoprotein-bound microRNAs. Arterioscler Thromb Vasc Biol 2013;33:1392–400.
[165] Tabet F, Vickers KC, Cuesta Torres LF, Wiese CB, Shoucri BM, Lambert G, et al. HDL-transferred microRNA-223 regulates ICAM-1 expression in endothelial cells. Nat Commun 2014;5:3292.
[166] Nazari-Jahantigh M, Wei Y, Noels H, Akhtar S, Zhou Z, Koenen RR, et al. MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. J Clin Invest 2012;122:4190–202.
[167] Guo JF, Zhang Y, Zheng QX, Zhang Y, Zhou HH, Cui LM. Association between elevated plasma microRNA-223 content and severity of coronary heart disease. Scand J Clin Lab Invest 2018:1–6.
[168] Qiu XK, Ma J. Alteration in microRNA-155 level correspond to severity of coronary heart disease. Scand J Clin Lab Invest 2018;78:219–23.
[169] Ishikawa H, Yamada H, Kondo K, Ota T, Yamazaki M, Ando Y, et al. Establishment of a simpler method for measuring HDL-microRNAs. Ann Clin Biochem 2018. https://doi.org/10.1177/0004563218775770.
[170] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for obesity management in adults. Obes Facts 2015;8:402–24.
[171] Kotsis V, Tsioufis K, Antza C, Seravalle G, Coca A, Sierra C, et al. Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part B: obesity-induced cardiovascular disease, early prevention strategies and future research directions. J Hypertens 2018;36:1441–55.
[172] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999–3058.
[173] American Heart Association. Scientific Sessions 2018; Final program. Available at: https://professional.heart.org/professional/EducationMeetings/MeetingsLiveCME/ScientificSessions/UCM_316900_Scientific-Sessions.jsp, Accessed date: 4 November 2018.
[174] Richard C, Couture P, Desroches S, Benjannet S, Seidah NG, Lichtenstein AH, et al. Effect of the Mediterranean diet with and without weight loss on surrogate markers of cholesterol homeostasis in men with the metabolic syndrome. Br J Nutr 2012;107:705–11.
[175] Książek M, Charmas M, Klusiewicz A, Zabielski P, Długołęcka B, Chabowski A, et al. Endurance training selectively increases high-density lipoprotein-bound sphingosine-1-phosphate in the plasma. Scand J Med Sci Sports 2018;28:57–64.